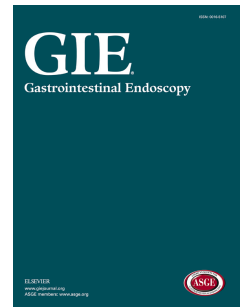


Accepted Manuscript

The “valley sign” in small and diminutive adenomas: prevalence, interobserver agreement, and validation as an adenoma marker

Douglas K. Rex, M.D, Prasanna Ponugoti, M.D., Charles Kahi, M.D



PII: S0016-5107(16)30668-X

DOI: [10.1016/j.gie.2016.10.011](https://doi.org/10.1016/j.gie.2016.10.011)

Reference: YMGE 10278

To appear in: *Gastrointestinal Endoscopy*

Received Date: 28 July 2016

Accepted Date: 2 October 2016

Please cite this article as: Rex DK, Ponugoti P, Kahi C, The “valley sign” in small and diminutive adenomas: prevalence, interobserver agreement, and validation as an adenoma marker, *Gastrointestinal Endoscopy* (2016), doi: 10.1016/j.gie.2016.10.011.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The “valley sign” in small and diminutive adenomas: prevalence, interobserver agreement, and validation as an adenoma marker

Douglas K. Rex, M.D., Prasanna Ponugoti, M.D., Charles Kahi, M.D.

Indiana University School of Medicine, Division of Gastroenterology and Hepatology
Indianapolis, IN

Address correspondence and reprint request to:

Douglas Rex, M.D.
Indiana University Hospital
4100 550 North University Blvd.
Indianapolis, IN
Phone: 317-948-8741
Fax: 317-944-5449
E-mail: drex@IU.edu

Abstract

Background: Classification schemes for differentiation of conventional colorectal adenomas from serrated lesions rely on patterns of blood vessels and pits. Morphologic features have not been validated as predictors of histology.

Aim: Describe the prevalence of the “valley sign” and validate it as a marker of conventional adenomas

Methods: Three experts judged the prevalence of the valley sign in 301 consecutive small adenomas. Medical students were taught to recognize the valley and tested on their recognition of the valley sign. Consecutive diminutive polyps were video-recorded and used to validate the association of the valley sign with conventional adenomas.

Results: The prevalence of the valley sign in 301 consecutive adenomas <10 mm in size, determined by 3 experts, ranged from 35% to 50%. Kappa values for agreement among the 3 experts were 0.557, 0.679, and 0.642. Ten medical students were taught to interpret the valley sign and recognized it with accuracy of 96% or higher in 50 selected photographs of diminutive polyps. Four medical students evaluated video-recordings of 170 consecutive diminutive polyps for the presence of the valley sign. Kappa values for the interpretation of the valley sign ranged from 0.52 to 0.68 among the students. The sensitivity of the valley sign for adenoma ranged from 40.2% to 54.9%, and specificity ranged from 90.2% to 91.7%. The valley sign was strongly associated with adenomas ($p < 0.0001$).

Conclusions: The valley sign is insensitive but highly specific for conventional adenoma in diminutive polyps. It may enhance classification schemes for differentiation of adenomas from serrated lesions based on vessels and pits.

Introduction

There are 2 major histologic classes of precancerous colorectal lesions, the conventional adenomas and the serrated class lesions. Pathologists in both academic and community centers are reasonably accurate and consistent at placement of colorectal lesions into these 2 categories¹. Subcategories of histology, including tubular versus villous and high grade versus low-grade dysplasia within the conventional adenomas², and hyperplastic polyp versus sessile serrated polyp within the serrated class³, are subject to considerable interobserver variation in pathologist interpretation.

Endoscopic criteria⁴ can also be used to reliably identify most precancerous colorectal lesions as belonging to the conventional adenoma versus serrated class⁵. Commonly used endoscopic criteria for differentiation of conventional adenomas from serrated class lesions use surface features such as the microvascular pattern and the shape of pits⁴. A feature that has been associated with conventional adenomas is a valley in the surface topography that appears red in white light and brown in narrow-band imaging (NBI) relative to the rest of the polyp surface (Figure 1)⁶. This valley is sometimes interpreted as a depression, but it differs from depression in that the edges of the valley

are sloping whereas the edges of a true depression usually fall very sharply. Unlike the true depression the valley depth does not extend to or below the level of the normal mucosa, and vascular pattern in the valley is consistently maintained without disruption. The valley sign also is distinct from pseudodepression, which is seen in some non-granular lateral spreading tumors, and which by definition are at least 10 mm in diameter⁷. The relatively red color in white light and the brown color in NBI appears related to a concentration of blood vessels in the valley. Again unlike the true depression, we refer to this feature as the “valley sign” (Figure 2).

This endoscopic sign (the “valley sign”) has not been used as a criterion for the diagnosis of adenomas in classification schemes for differentiation of conventional adenomas from serrated class lesions⁴. In this report, we describe the prevalence of the valley sign in conventional adenomas, describe interobserver variation between experts and novices in identification of the valley sign, and validate the valley sign as a marker of adenomatous histology in diminutive colorectal polyps.

Methods

All aspects of the study were conducted using de-identified photographs and videos. Because all the photographs and videos existed before initiation of the study, this study

was granted exempt status by the Indiana University Human Research Committee on October 9, 2015.

The first goal was to establish the prevalence of the valley sign in conventional adenomas as determined by experienced endoscopists and to determine their interobserver agreement in identifying the sign.

The prevalence of the valley sign in small adenomas was previously estimated at 15%⁶. However, improvements in technology may have led to enhanced recognition of this feature. We estimate the prevalence of the valley sign to be up to 25% of small adenomas and set the precision of the estimate of prevalence at 5%. These parameters require a sample size of 289 adenomas < 1 cm in size.

We used a library of consecutively photographed colorectal adenomas polyps < 1 cm in size previously developed by D.K.R. to retrieve a sample of 301 consecutive pathologically verified adenomas < 1 cm in size. Three individuals experienced in NBI and polyp differentiation independently evaluated the photographs and determined whether each individual polyp demonstrated the valley sign. Agreement among the 3 independent observers was determined using Kappa statistics.

In the second portion of the study, we tested whether endoscopy naive individuals could be trained to identify the valley sign in selected samples. The study subjects were

10 first and second year medical students at Indiana University without experience in endoscopy. In a single session, the medical students were shown a sample of 15 selected diminutive polyps (≤ 5 mm), including 5 pathologically verified hyperplastic polyps, and 10 conventional adenomas, 5 of which were judged by the endoscopy experts to have the valley sign, and 5 of which were judged to not have the valley sign. The medical students were taught to recognize the valley sign, without reference to the histology of polyps. No information was given regarding polyp histology or any other surface feature that identifies adenomas or hyperplastic polyps⁴. After the teaching session, the medical students were immediately shown 50 additional polyps in random order, including 16 verified hyperplastic polyps, and 34 verified conventional adenomas, of which 17 were judged to have a definite valley sign and 17 of which were judged to definitely not have the valley sign. The medical students were asked to record for each polyp whether or not it demonstrated the valley sign. To determine the sample size for this portion of the study we assumed a kappa of 0.70. A 95% confidence interval for kappa will extend at most ± 0.15 (from 0.55 to 0.85) with 50 images evaluated by each the 10 medical students, where 1/3 of the images are adenomas with the valley sign, 1/3 of the images are adenomas without the valley sign, and 1/3 of the images are hyperplastic polyps without the valley sign.

For the validation step we used a library of videos of 170 consecutive diminutive polyps removed by D.K.R. Each video was approximately 5 to 15 seconds in length, and included at least 1 short segment with the image frozen. Videos were recorded only in

narrow-band imaging. The study subjects included 4 of the 10 medical students who had been trained to identify valleys in the second part of the study. Throughout the study the students remained naïve to the purpose of the study. The concepts of histology in general and adenoma vs. serrated lesion specifically were never discussed with the students. Neither the NICE (NBI International Colorectal Endoscopic Classification) classification nor any other endoscopic feature predictive of histology was discussed with the students.

For the validation step, we estimated the prevalence of the valley sign to be 50% in adenomas. For a 95% confidence interval to determine the true prevalence with a margin of $\pm 8\%$, a sample of 160 polyps was needed.

We used the chi-square test to compare binary variables. General estimating equation (GEE) methods were used to test the overall association between the student's identification of the valley sign and the pathologist's interpretation of histology as well as the endoscopist's prediction of histology.

Results

Prevalence of the valley sign in adenomas

For part 1 of the study, the sample consisted of 301 consecutive polyps < 10 mm in size by endoscopy and which were pathologically verified as conventional adenomas. Thirty-

five adenomas were judged to be 6 to 9 mm in size, and the remainder (n = 266) were ≤ 5 mm in size.

Of the 301 polyps for photograph of part one, 170 were photographed with using HCF 180 colonoscopes, and 131 were photographed using HCF 190 colonoscopes. There were no differences in the study results between the 180 and 190 instruments so the results are presented in combined form. Figures 1 through 5 show diminutive adenomas with the valley sign photographed in white light and narrow-band imaging with and without the valley delineated on the photograph.

The overall prevalence of the valley sign as determined by the 3 experts is shown in Table 1. The prevalence of a definite valley ranged from 35% to 50% for the 3 endoscopists. The weighted kappas for reviewer 1 versus 2, 1 versus 3, and 2 versus 3 for the entire data set were 0.557, 0.679, and 0.642, respectively, indicating moderate to substantial agreement for identification of the valley sign.

Identification of the valley sign by novices in selected polyps

Unlike the polyps used for part 1, the polyps used for part 2 were selected polyps and 1/3 of the lesions were hyperplastic. After the brief educational session, the 10 medical students scored the 50 selected diminutive polyps for valleys with an overall correct

answer rate of 98.6%. Six of the 10 students correctly scored all of the 50 polyps, and no student missed more than 2 polyps.

Validation of the valley sign as a marker of adenomas

Four medical students were shown 170 consecutively videorecorded diminutive polyps. Of the 170 consecutive polyps, 82 were identified by our pathologist as conventional adenomas, 61 were identified as serrated class lesions (hyperplastic=58 and sessile serrated polyp=3), and 27 were identified as normal mucosa. We did not systematically have the slides read as normal mucosa re-cut by the pathologists. For calculation of the student performance against the criterion standard of pathology, we excluded the 27 polyps identified by our pathologists as normal tissue. None of the lesions with or without the valley sign had high-grade dysplasia or villous elements.

Table 2 shows the kappa values and percent agreement with regard to the presence of valleys among the students. Again, the kappa values were in the moderately good to substantial range.

Table 3 shows the prevalence of valleys as recorded by the 4 medical students according to the final pathology report. The prevalence of valleys ranged from 40.2% to 54.9% for the 4 medical students. The prevalence of valleys in hyperplastic polyps ranged from 8.3% to 9.8%. Thus, the valley sign had high specificity for adenomas.

Table 4 shows the performance of the 4 medical students according to the endoscopic prediction of the pathology of all 170 lesions as predicted by the endoscopist who captured the videos (D.K.R.). The range of prevalences of valleys within adenomas was comparable in this analysis to the analysis using pathology as the criterion standard, and the specificities and positive predictive values were numerically higher than in the pathology criterion standard analysis.

For each student and for all students combined the interpretation of the valley sign and conventional adenoma was strongly associated ($p < 0.0001$). This was true using the pathology report or the endoscopist's prediction as the criterion standard for adenomas.

Figures 6 through 8 show examples of diminutive adenomas in the validation sample for which the 4 students agreed there was a valley sign (Figure 6), for which they agreed there was no valley sign (Figure 7), or for which there was disagreement among the students regarding whether the valley sign was present (Figure 8)

Discussion

In this report, we described the association of the "valley sign" with colorectal adenomas and validate the valley sign as a predictor of adenomatous histology in diminutive colorectal polyps. The sensitivity of the valley sign varied from 35% to 50% among 3 experts in polyp differentiation, and the prevalence in adenomas was similar

(40-55%) when consecutive diminutive polyps were evaluated by novices. Thus, the sensitivity of the valley sign for adenomatous histology was low. On the other hand, the positive predictive value of the valley sign approached 90% in the endoscopic novices, and the specificity was above 90%. Thus, when the valley sign is present, it is a reliable predictor of adenoma. We did not evaluate the use of the valley sign in combination with other features of adenomas, such as those specified by the NICE classification. Additional investigation could determine whether the valley sign adds value above the features of the NICE classification.

The anatomic basis for the valley sign is currently uncertain. The red color of the valley in white light and darker brown color in NBI appear related to a concentration of relatively punctate vessels in the valley with magnified endoscopic inspection. Detailed sectioning and histologic analysis should be informative for understanding the anatomic basis of the valley sign. In our experience the valley sign is not associated with either high-grade dysplasia or villous elements in adenomas but interpretation of these histologic elements in small adenomas is associated with poor interobserver agreement among pathologist². The valley sign is different from “pseudodepression,” which is seen in some non-granular lateral spreading tumors⁷.

We validated the valley sign as a marker of diminutive adenomas in novices to avoid any bias that might be introduced by the expected knowledge of other aspects of endoscopic polyp analysis among experts. However, we found that experts identified a

prevalence for the valley sign in one sample of small and diminutive adenomas (35%-50%) that was comparable to the fraction of diminutive adenomas with a valley (40%-55%) identified by 4 novice medical students. Additional study of the utility of the valley sign for expert endoscopists is warranted. Further, the current study was performed using NBI, though anecdotally we commonly recognize the valley sign in white light. Whether the use of the valley sign has comparable performance in white light and NBI, and the utility of the valley sign when evaluated by *iscan* (Pentax, Montvale, NJ) and Fujinon Intelligent Chromo Endoscopy (Fujifilm, Tokyo, Japan), warrants investigation.

In summary, we have validated the valley sign as a predictor of colorectal adenomas, and suggest that the valley sign be taught to endoscopists as a predictor of adenomas, and that its value in evaluation of strategies such as resect and discard⁸ be considered in additional investigations.

References

1. Rex DK, Alikhan M, Cummings O, Ulbright TM. Accuracy of pathologic interpretation of colorectal polyps by general pathologists in community practice. *Gastrointest Endosc* 1999;50:468-74.
2. Lasisi F, Mouchli A, Riddell R, et al. Agreement in interpreting villous elements and dysplasia in adenomas less than one centimetre in size. *Dig Liver Dis* 2013;45:1049-55.
3. Khalid O, Radaideh S, Cummings OW, O'Brien MJ, Goldblum JR, Rex DK. Reinterpretation of histology of proximal colon polyps called hyperplastic in 2001. *World J Gastroenterol* 2009;15:3767-70.
4. Hewett DG, Kaltenbach T, Sano Y, et al. Validation of a simple classification system for endoscopic diagnosis of small colorectal polyps using narrow-band imaging. *Gastroenterology* 2012;143:599-607 e1.
5. Patel SG, Schoenfeld P, Kim HM, et al. Real-Time Characterization of Diminutive Colorectal Polyp Histology Using Narrow-Band Imaging: Implications for the Resect and Discard Strategy. *Gastroenterology* 2016;150:406-18.
6. Rex DK. Narrow-band imaging without optical magnification for histologic analysis of colorectal polyps. *Gastroenterology* 2009;136:1174-81.

7. Kudo S, Lambert R, Allen JI, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc* 2008;68:S3-47.
8. Rex DK, Kahi C, O'Brien M, et al. The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2011;73:419-22.

Table 1. Prevalence of the valley sign in 301 consecutively photographed adenomas < 1 cm in size.

	Endoscopist 1	Endoscopist 2	Endoscopist 3
Valley present	104(35)*	150(50)	124(41)
Uncertain	22(7.3)	15(5.0)	16(5.3)
Valley absent	175(58)	136(45)	161(53)

*number (percent)

Table 2. Kappa statistics and % agreement for 4 medical students' identification of the valley sign in 170 consecutive diminutive polyps

	Kappa	Percentage Agreement
Student 1 vs. 2	0.68	85.88
Student 1 vs. 3	0.65	84.12
Student 1 vs. 4	0.66	84.62
Student 2 vs. 3	0.52	79.41
Student 2 vs. 4	0.56	81.07
Student 3 vs. 4	0.57	80.47

Table 3. Identification of the valley sign by 4 medical students in 143 consecutive diminutive colorectal polyps with pathologic confirmation of histology

	Sensitivity for adenomas	Specificity	PPV	NPV
Student 1	54.9%	90.2%	88.2%	59.8%
Student 2	40.2%	90.2%	84.62%	52.3%
Student 3	52.4%	90.2%	87.8%	58.5%
Student 4	48.8%	91.7%	88.9%	56.7%

Table 4. Identification of valley sign in all 170 patients using the colonoscopist's (D.K.R.) endoscopic prediction of histology as the criterion standard

	Sensitivity	Specificity	PPV	NPV
Student 1	58.2%	93.1%	92.0%	62.0%
Student 2	42.9%	91.7%	87.5%	54.1%
Student 3	56.2%	94.4%	93.2%	61.3%
Student 4	52.0%	93.0%	91.1%	58.4%

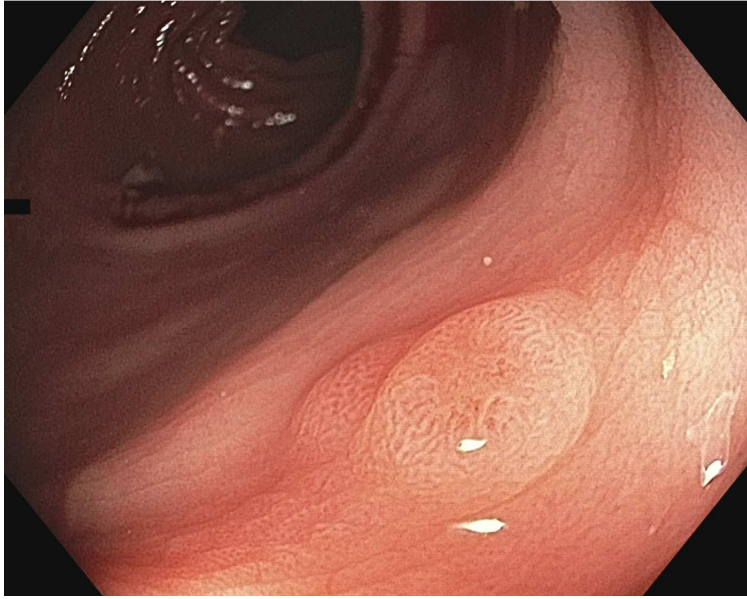
Figure Legends

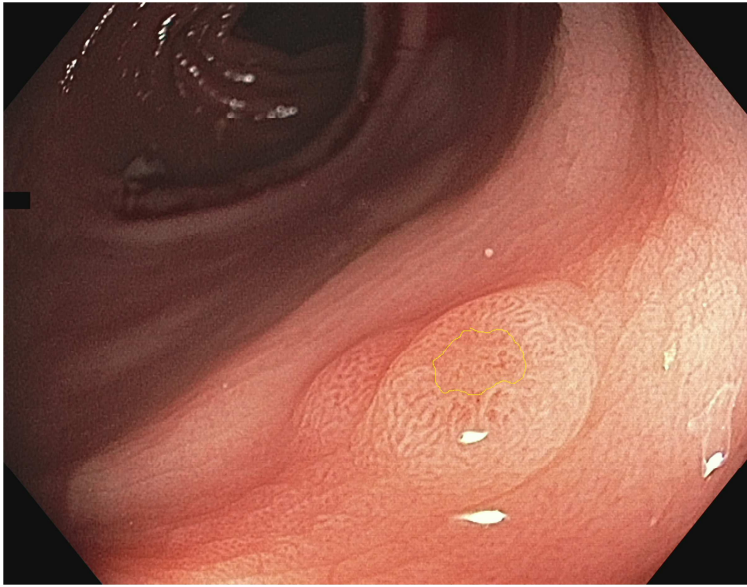
Figure 1-5. In each figure "a" is a white light photograph and "c" is a narrow-band imaging photograph of a diminutive adenoma showing the valley sign. In each figure "b" and "d" are the same photographs shown in "a" and "c," respectively, but with the margin of the valley delineated by a yellow line.

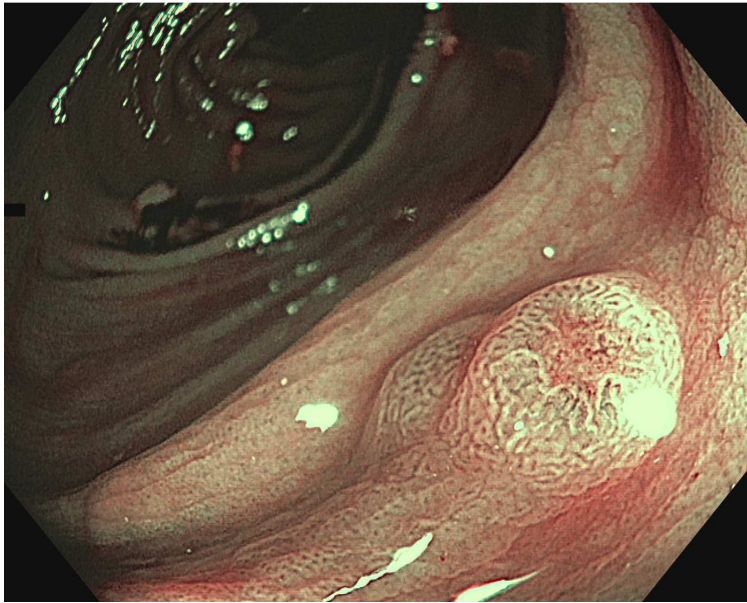
Figure 6a-c Narrow-band imaging photographs of 3 adenomas from the sample of 170 consecutive diminutive polyps that each of 4 medical students agreed did not have the valley sign.

Figure 7a-c Narrow-band imaging photographs of 3 adenomas from the sample of 170 consecutive diminutive polyps that each of the 4 medical students agreed did have the valley sign.

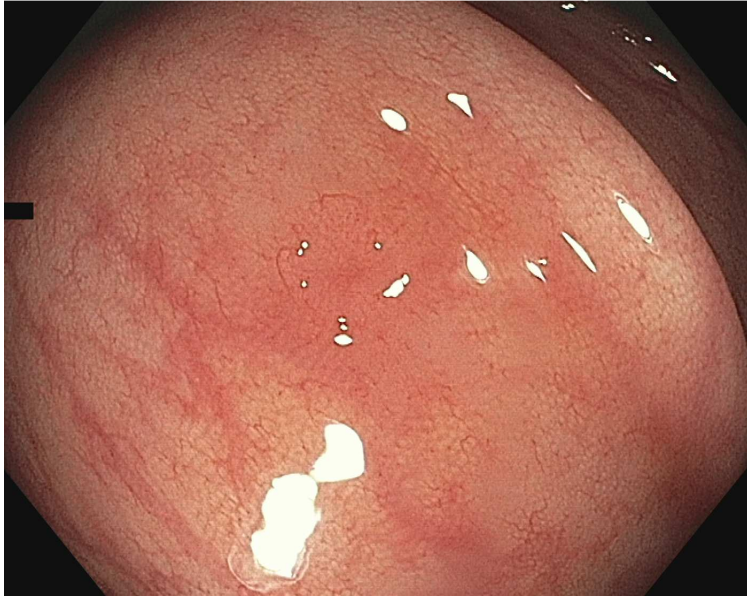
Figure 8a-c Narrow-band imaging photograph of 3 adenomas from the sample of 170 consecutive diminutive polyps that 2 of the 4 medical students considered did and 2 considered did not have the valley sign.

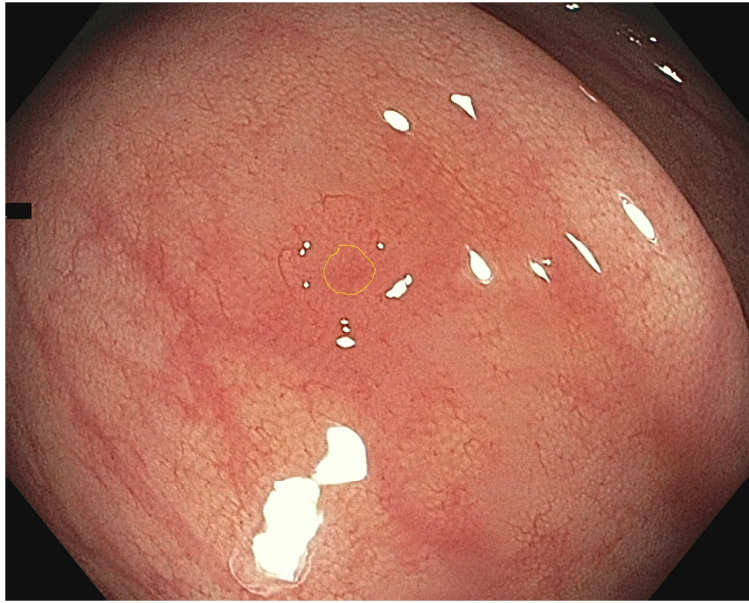


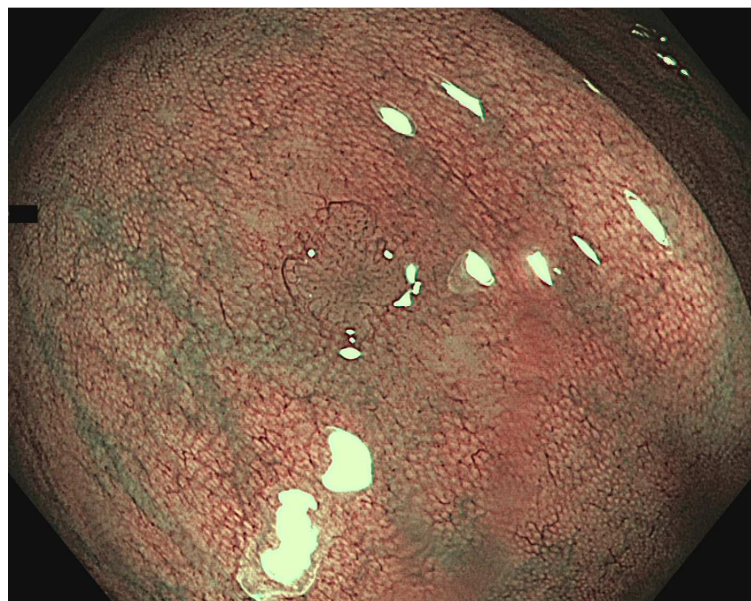


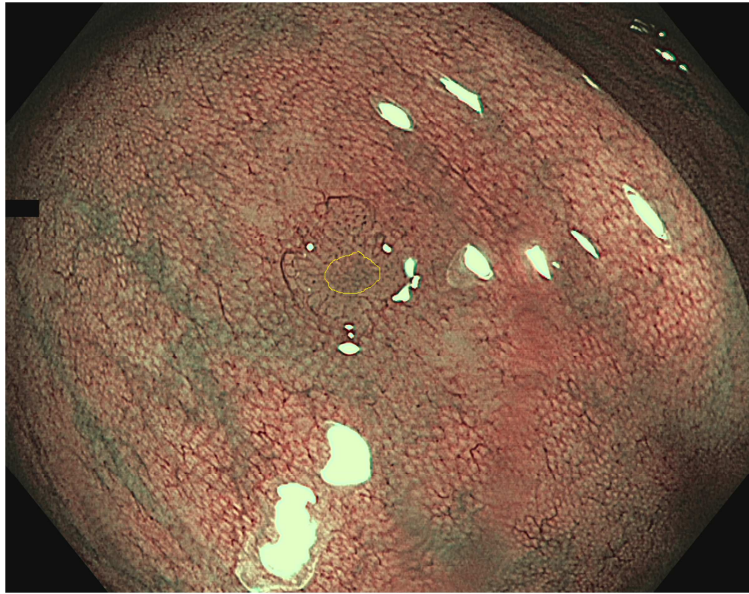


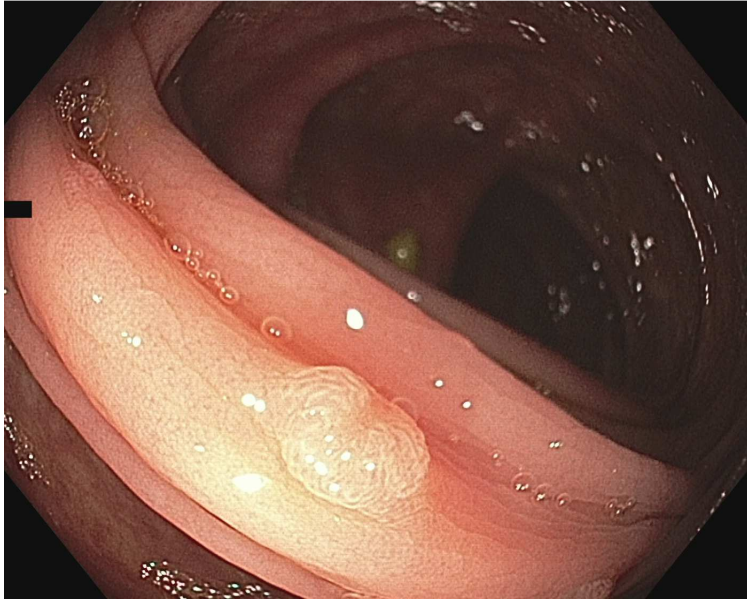


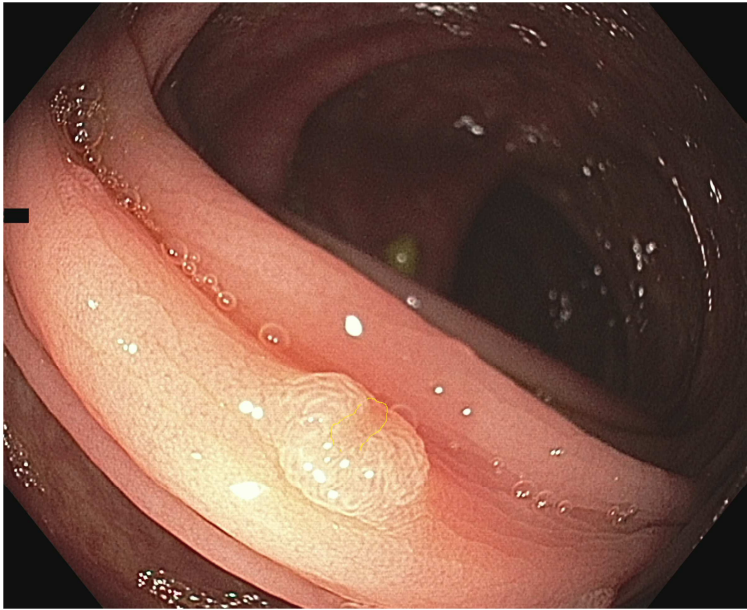


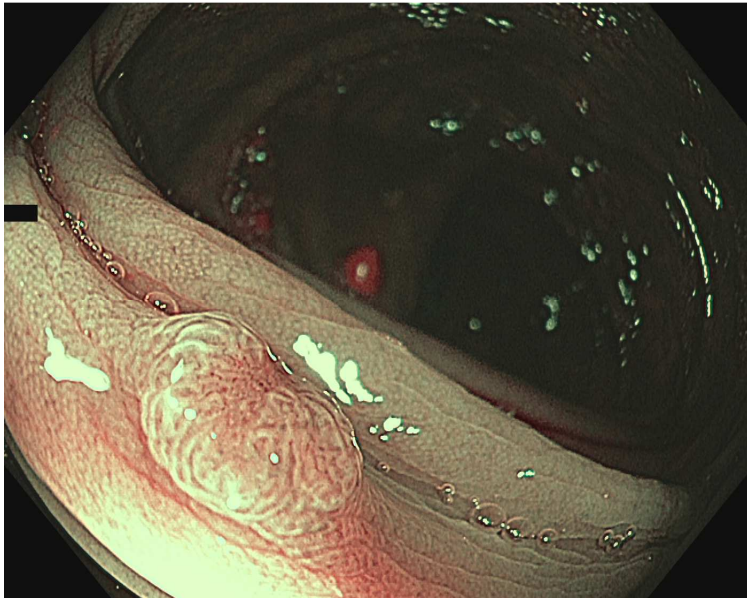


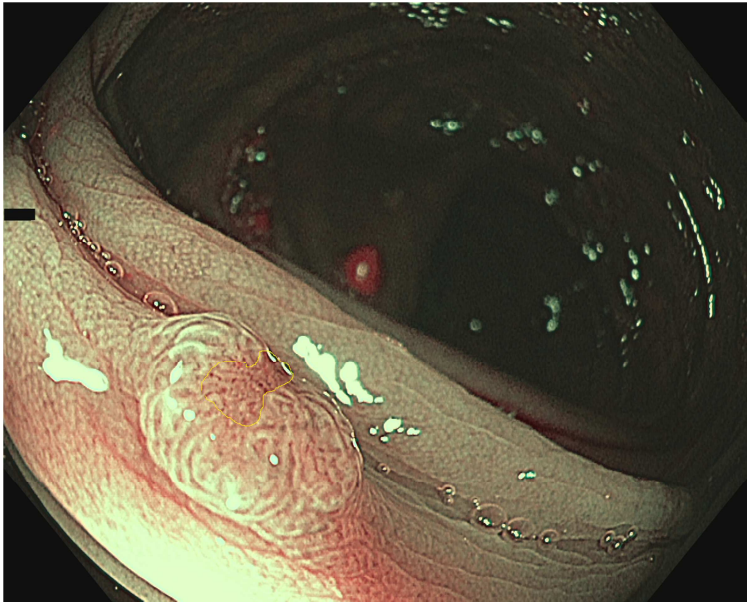








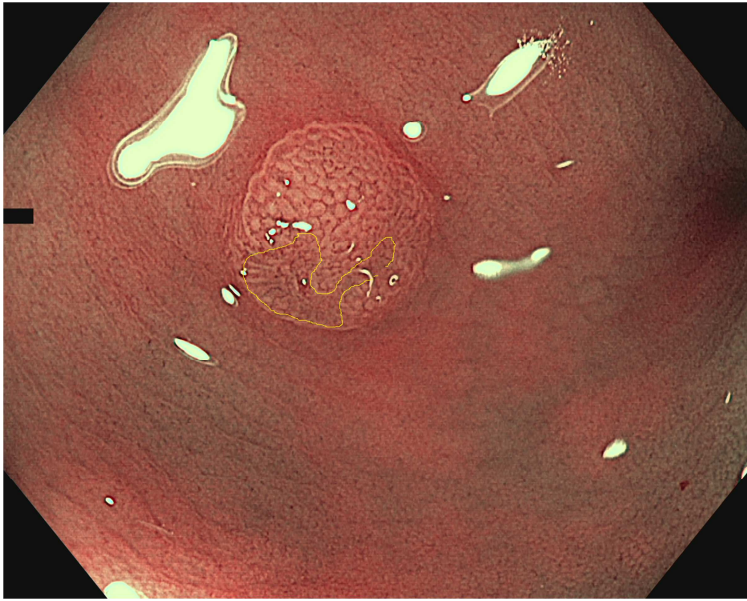


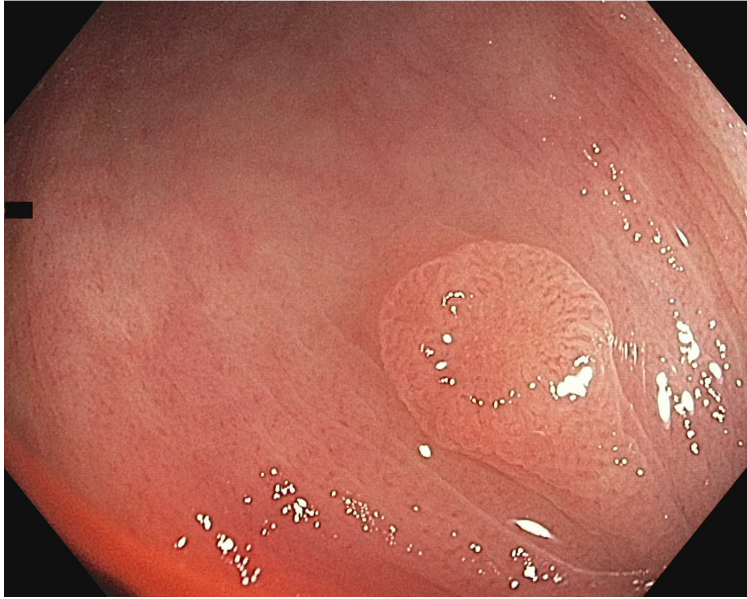


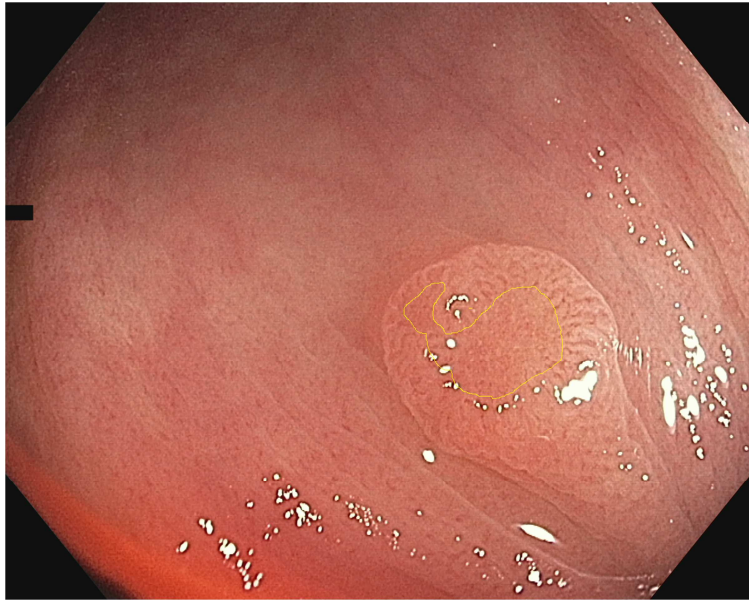




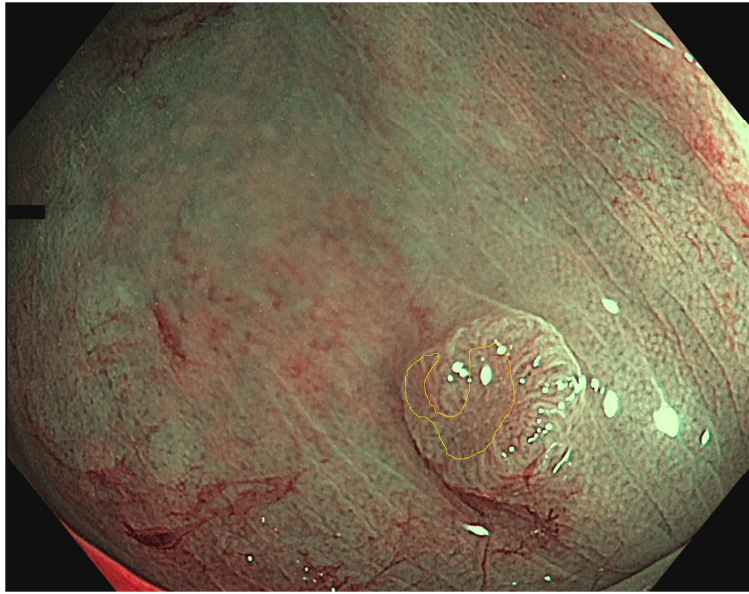


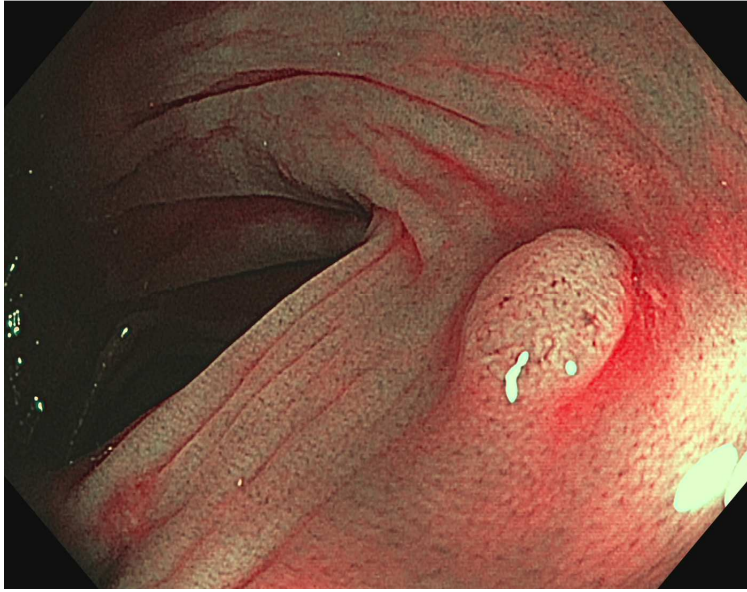






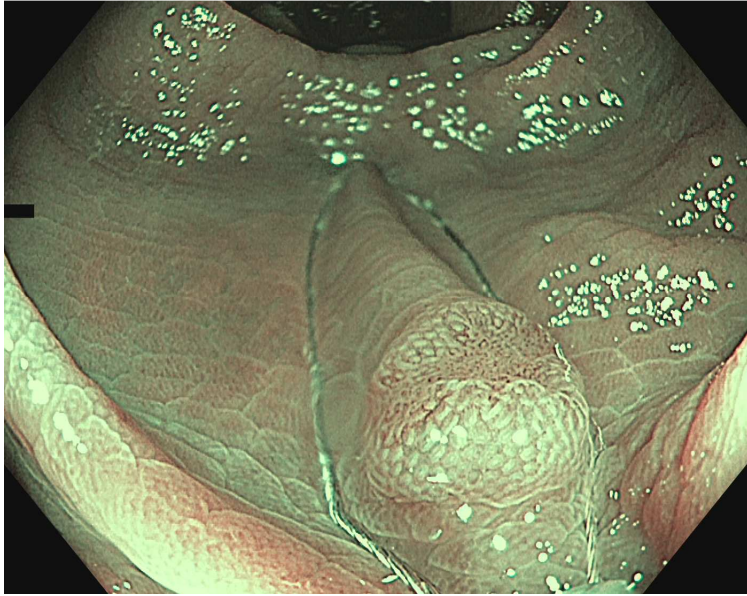


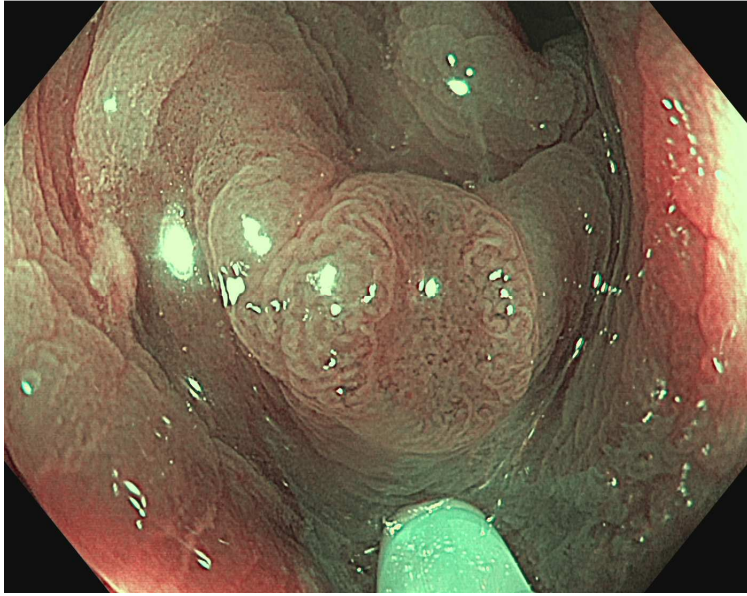


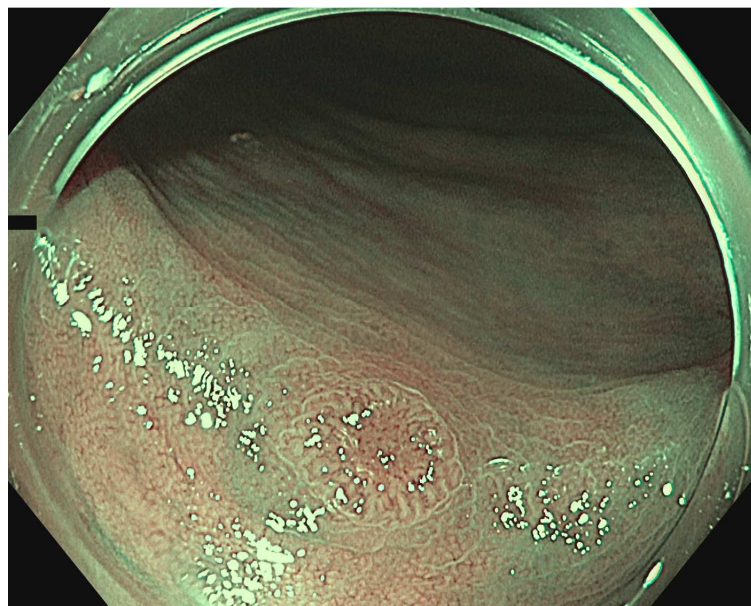


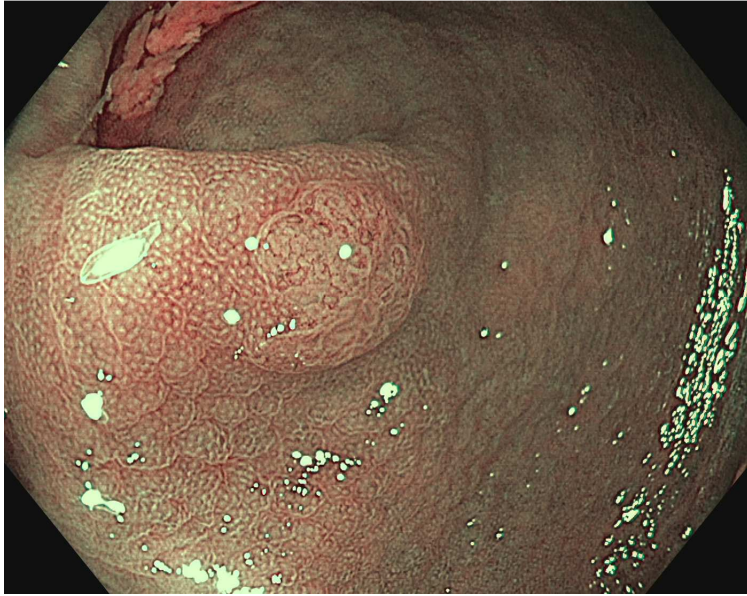


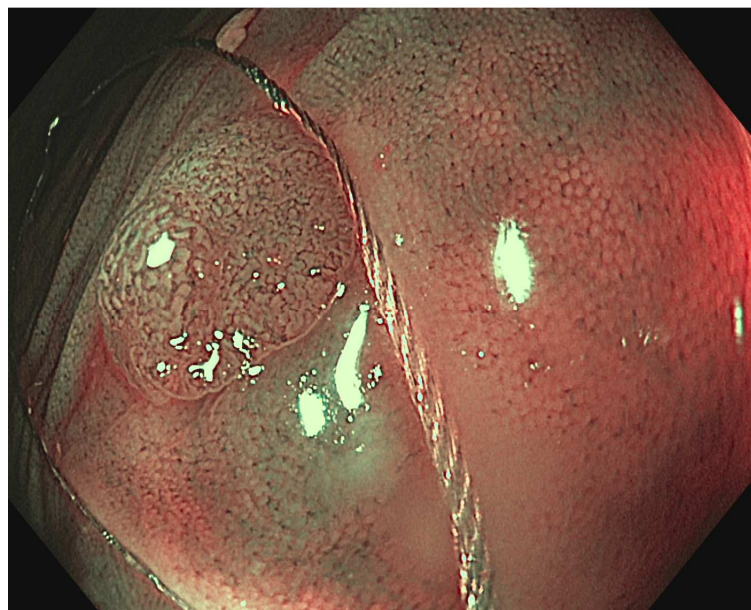














Acronyms:

mm: Millimeters

NBI: narrowband imaging

cm: centimeters

DKR: Douglas Kevin Rex

NICE: NBI International Colorectal Endoscopic Classification

GEE: general estimating equation

PPV: positive predictive value

NPV: negative predictive value